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Systematic Review of Granulomatous Invasive Fungal Sinusitis Management

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ABSTRACT

Objectives: Granulomatous invasive fungal sinusitis (GIFS) affects immunocompetent individuals. There is ongoing debate over whether surgery, antifungal medication, or a combined approach is the best treatment. This article summarizes reports about GIFS and its management.

Methods: Eight search engines, gray literature, and review articles were searched. Two independent reviewer groups screened the eligibility of articles. An independent reviewer solved disagreements. Exclusion criteria included non-English language reports, papers with unavailable full-texts, reviews, publications before 1980, and studies lacking information about GIFS management.

Results: Of the 279 identified articles, 41 studies were included ($n = 89$ patients). Sinonasal GIFS with skull-base/intracranial extension was associated with an increase in mortality ($p = 0.002$, OR = 14.083; 95% CI = 1.753–113.157). Treatment was associated with an 87.2% remission rate ($p < 0.001$, OR = 7.818; 95% CI = 4.502–13.576); a combined medical and surgical approach had a 74.2% recovery rate. Of surgical interventions, the highest recovery rates were associated with endoscopic debulking (52.5%), extensive surgical debulking (32.5%), and open sinonasal approach (15%, $p = 0.132$). The utilization of voriconazole was associated with higher recovery rates, but this was not significant (76.9 vs. 56%, $p = 0.548$).

Conclusion: Sinonasal GIFS with skull-base/intracranial extension is associated with higher mortality rates. The superiority of the endoscopic debulking and voriconazole protocol in managing these cases warrants further investigation.

Level of Evidence: Level 4.

1 | Introduction

Invasive fungal sinusitis (IFS) is a debated topic due to a lack of formal consensus on clinical classification, diagnostic criteria, and management approach. DeShazo et al. published diagnostic criteria that classify IFS according to clinical and histopathological evidence into acute fulminant, chronic invasive, and granulomatous invasive fungal sinusitis (GIFS) [1].

GIFS is also known as indolent fungal sinusitis [2–5]. Most cases arise in primarily dry climates such as Pakistan, India, Saudi Arabia, and China and less frequently in Western countries, indicating potential geographical, ethnic, or environment-related aspects [6–9]. GIFS typically presents with insidious sinus disease and proptosis, mainly in immunocompetent patients [2, 10, 11]. In contrast to other types of IFS, *Aspergillus flavus* is the pathogen most exclusively

isolated in GIFS. It drives the formation of non-caseating granuloma with local tissue invasion [10, 11]. If not properly managed, it can extend to the dura and brain, leading to devastating outcomes.

Most data on GIFS come from retrospective case reports or case series [12]. There is ongoing debate on the appropriate management of these cases. It is unclear whether a surgical approach and/or antifungal medication is the best treatment modality, due to the limited available evidence. The lack of standardized reporting further complicates the process of making evidence-based management decisions for GIFS cases. This systematic review aims to summarize published reports about GIFS and its management.

2 | Materials and Methods

This systematic review was conducted in accordance with the PRISMA protocol [13]. An expert medical librarian searched PROSPERO, Medline, EMBASE, Cochrane Library, CINAHL, SCOPUS, ProQuest Dissertations, and Theses Global with the terms "chronic granulomatous," "sinus," and "fungus," up until September 24, 2020 (Appendix 1). Gray literature and review articles were also searched. A PICO table is included (Appendix 2).

2.1 | Study Eligibility, Inclusion, and Exclusion Criteria

The screening was performed according to the DeShazo criteria classification of GIFS [1]. Two pairs of independent reviewers assessed the studies for eligibility. An independent reviewer resolved any disagreements. Studies published before 1980, reviews, non-English articles, and those with unavailable full texts were excluded.

2.2 | Data Extraction and Quality Assessment

The same screening process was used to extract data from each paper. A preset form was used to extract the following data: demographics, immune status, comorbidities, disease extension, fungal species, radiological and histopathological findings, medical treatment, surgical treatment, and outcomes. The Joanna Briggs Institute (JBI) critical appraisal checklist for case reports was used to assess the quality of studies [14].

2.3 | Reporting of Results

GIFS disease extension was classified as a sinonasal disease, a sinonasal disease with orbital extension, or sinonasal disease with skull-base/intracranial extension (regardless of orbital involvement). Notably, we grouped intracranial extension along with skull-base extension to overcome poor reporting of disease extension, lack of appropriate imaging, or poor imaging quality in the included studies, all of which obscure accurate identification of disease extension.

Treatments were classified as medical, surgical, or combined intervention. Medical interventions were subclassified as voriconazole or other antifungal medication (including amphotericin B, caspofungin, and others) [15]. Surgical interventions were subclassified as endoscopic sinonasal debulking, open sinonasal debulking, or extensive open debulking (i.e., exploration of orbital contents or cranial structures). Finally, outcomes were classified as recovery, death, or residual.

2.4 | Statistical Analysis

Basic descriptive and inferential statistics were applied including the chi-squared and Fisher's exact test, and odds ratios. Results were considered significant at $p < 0.05$.

3 | Results

3.1 | Identification of Eligible Studies and Cohort Characteristics

Of 279 relevant studies, 41 articles were eligible, as shown in the PRISMA flow chart (Figure 1). The final cohort is a total of 89 patients, of which 54% were female (Table 1) [6, 12, 16–55]. The age at diagnosis was 41.8 ± 15.31 years. In the majority of patients, GIFS had extended to either the orbit ($n = 25$) or skull-base/intracranial structures ($n = 49$). Patients received combined treatment (74.2%), medical (13.5%), or surgical intervention (9%). Fifty-one out of 89 patients recovered.

3.2 | Does Disease Extension Impact the Outcome?

The mortality rate was approximately 14 times higher in skull-base/intracranial extension (26.5%) compared to those without such extension (2.5%) ($p = 0.002$, OR = 14.083; 95% CI = 1.753–113.157) (Table 2). Furthermore, the mortality rate for purely sinonasal disease was 6.7% versus zero mortality in sinonasal with orbital extension ($p = 0.191$). The extension of GIFS is, therefore, associated with higher mortality ($p = 0.007$).

3.3 | Should These Patients Receive an Intervention?

Morality was prevented in 87.2% of treated patients, whereas all three patients who did not receive any intervention died ($p < 0.001$, OR = 7.818, 95% CI = 4.502–13.576). For skull-base/intracranial extension in particular, treated patients had a lower mortality rate than untreated patients ($p = 0.016$, OR = 4.273; 95% CI = 2.547–7.167).

3.4 | Which Intervention Results in Better Outcomes?

Recovery rates for combined medical and surgical interventions were 60.6%, 58.3%, and 50%, respectively ($p = 0.930$). In the combined intervention group, endoscopic sinonasal debulking, open sinonasal debulking, and extensive open surgery had treatment success rates of 52.5%, 15%, and 32.5%, respectively ($p = 0.132$); the recovery rate was nonsignificantly higher among skull-base/

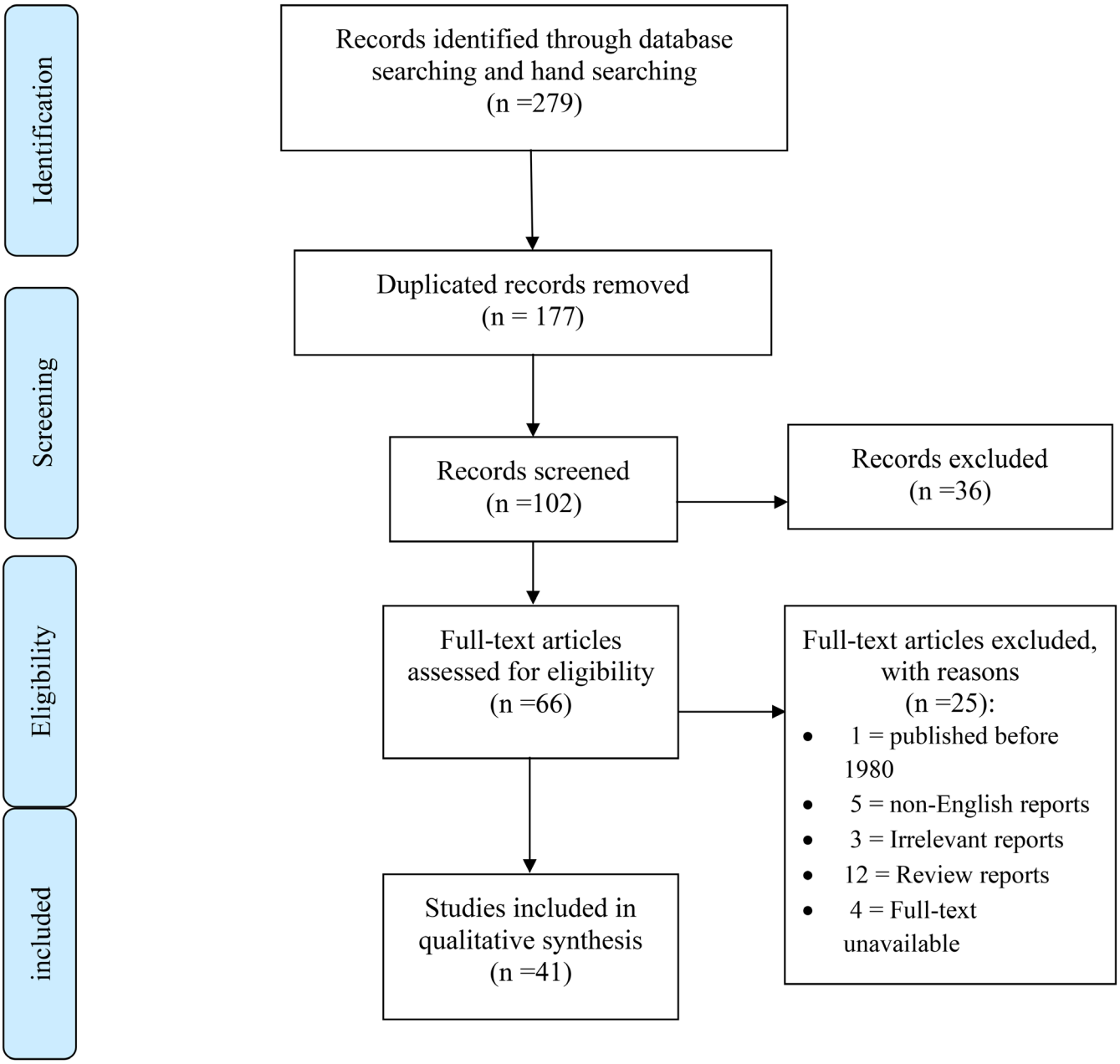

FIGURE 1 | PRISMA diagram detailing the article selection process for further evaluation and inclusion.

intracranial extension patients who were managed with extensive surgery (63.2%). Voriconazole had a higher recovery rate of 76.9% versus 56% for other antifungal treatments, but this was not statistically significant ($p = 0.548$), as shown in Table 3. Moreover, a combined intervention was especially beneficial in those with sinonasal disease extending to the orbits, with a recovery rate of 77.8%.

4 | Discussion

This review describes the current management of GIFS as reported in peer-reviewed studies. GIFS is a chronically indolent form of IFS that requires prompt diagnosis and intervention before significant morbidity or mortality ensues. This review revealed three cases where patients died without receiving any intervention [16, 25, 36]. This might be explained by late presentation with extensive disease and/or death before intervention. In 87.2% of cases, mortality was prevented by any intervention, regardless of its type (medical, surgical, or combined).

Extension of GIFS beyond the sinonasal aspect increases the mortality risk. The mortality rate in sinonasal disease with skull-base/intracranial extension (26.5%) was higher than in those with only sinonasal disease (6.7%) or sinonasal with orbital extension (0%). In the single case of death with sinonasal disease, mortality was due to systemic illness rather than GIFS. This outcome was attributed to misdiagnosis at presentation and iatrogenic immunosuppression. The mortality risk associated with sinonasal disease is, hence, lower than that of sinonasal disease extending to the orbit or skull-base/intracranial structures.

TABLE 1 | Demographic characteristics.

Cases	*N* = 89
Gender	
M	41 (46.1%)
F	48 (53.9%)
Age (mean ± SD)	41.8 ± 15.31
Immunocompetent	82 (92.1%)
DM	7 (7.9%)
Sinonasal disease	15 (16.9%)
Sinonasal with orbital extension	25 (28.1%)
Sinonasal with skull-base/intracranial ± orbital extension	49 (55.1%)
Pterygopalatine fossa extension	12 (13.5%)
Infratemporal fossa extension	7 (7.9%)
Cheek extension	2 (2.2%)
Palate extension	1 (1.2%)
Received intervention (medical, surgical, or combined)	83 (96.6%)
Medical	12 (13.5%)
Surgical	8 (9%)
Combined	66 (74.2%)
Surgical intervention	
Endoscopic debulking	35 (39.3%)
Open approach	13 (14.6%)
Extensive	26 (29.2%)
Medical intervention	
Voriconazole	14 (15.7%)
Other antifungal medication	64 (71.9%)
Outcomes	
Cured	51 (57.3%)
Residual	24 (27%)
Death	14 (15.7%)

Abbreviations: DM, diabetes mellitus; F, female; M, male; SD, standard deviation.

Fungal sinusitis is a clinically diverse entity. Fulminant invasive sinusitis has rapid progression to vital structures. Aggressive medical and surgical approaches are the treatment of choice for this condition [56]. GIFS, on the other hand, is indolent in nature and occurs mainly in immunocompetent people. There is an ongoing debate on which intervention is best for GIFS, whether the intervention should be tailored based on the presence of extra-sinus extension, and whether an aggressive or minimal intervention approach is optimal. The data included in this review reveals that combined medical and surgical management shows a higher success rate than either modality alone. GIFS has traditionally been managed with extensive open surgery and antifungal medications [17, 23]. This review found that this approach has no outcome benefit over endoscopic sinonasal debulking with antifungal medication and, in fact, has a lower success and higher mortality rate. Therefore, a recommendation of minimal surgical techniques, such as endoscopic sinonasal debulking, is supported to promote an increased recovery rate and decrease the risk of complications that follow extensive open surgery.

The use of amphotericin B carries a high risk of renal complications and has a lower recovery rate than voriconazole [57, 58]. Patterson et al. and Herbrecht et al. found that patients with invasive aspergillosis who received voriconazole alone responded well and had better outcomes compared to those receiving amphotericin B with or without additional antifungal medications (hazard ratio of 59%; 95% CI = 0.40–0.88) [57]. In addition to the significant risk of renal impairment, amphotericin B was associated with a higher rate of hypokalemia and systemic events such as fever, chills, or anaphylaxis [57]. On the other hand, voriconazole has been found to be associated with self-limiting hallucinations and visual disturbances, but not to a significant degree [57]. Unlike amphotericin B, voriconazole can be given orally, reducing the need for hospitalization [35]. However, a major drawback of voriconazole is that it costs more than amphotericin B; this is notable as most cases arise in developing countries. Overall, voriconazole could be recommended as a first-line antifungal for the treatment of GIFS, considering its benefits and drawbacks, based on our preliminary evidence and the international clinical practice guidelines established by the Infectious Diseases Society of America [58].

This systematic review has some limitations. Only 89 relevant cases of GIFS could be included, which could be attributed to the rarity of the disease or underreporting. The cited cases are extracted solely from retrospective studies and case series, as these are the only available reports in the literature. The findings of this review need to be validated in a more targeted and organized study to help establish a management protocol for this serious disease.

In conclusion, GIFS with skull-base/intracranial extension is associated with an increased risk of mortality. Higher quality research is needed to better evaluate the efficacy of different interventions for GIFS.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

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TABLE 2 | Association between presence of extension and outcome in CGIFS.

Skull-base/intracranial extension	Death (%)	*p*	Odds ratio	95% Confidence interval
No	1 (2.5)	**0.002***	14.083	1.753–113.157
Yes	13 (26.5)			
Extension	**Death (%)**	***p***	**Odds ratio**	**95% Confidence interval**
Sinonasal disease	1 (6.7)	0.191	0.933	0.815–1.069
Sinonasal with orbital extension	0			

*Bolded value indicates statistically significant results ($p < 0.05$).

TABLE 3 | Relationship between outcome, surgery, and medical treatment.

Surgical intervention	Outcome (%)			*p*
	Cured	Residual	Death	
Endoscopic	21 (52.5)	8 (47.1)	3 (33.3)	0.132
Open	6 (15)	5 (29.4)	0	
Extensive	13 (32.5)	4 (23.5)	6 (66.7)	
Medical treatment	**Outcome (%)**			***p***
	Cured	**Residual**	**Death**	
Voriconazole	10 (76.9)	2 (15.4)	1 (7.7)	0.548
Other antifungal medication	28 (56)	14 (28)	8 (16)	

Note: $p < 0.05$ indicates statistically significant results ($p < 0.05$).

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.